The need for more translational preclinical models of Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune neuroinflammatory disorder with an unpredictable and variable course. There is no curative therapy currently available for MS, but a handful of drugs targeting the autoimmune component are used primarily to manage flare-ups. Recently, a new breakthrough drug (ocerlizumab) was approved for primary progressive MS as well as relapsing-remitting MS, but there is still an unmet clinical need for the more debilitating forms of MS.

Drug discovery efforts to develop new therapies for progressive MS are challenged by the lack of preclinical animal models that recapitulate disease progression. This shortage is due in large part to the complexity of the disease pathology: four major disease categories have been identified with varying degrees of progression and symptomatic phenotypes – relapsing-remitting MS characterised by flare-ups and remissions of symptoms; secondary progressive MS that may develop in some relapsing-remitting MS patients and is characterised by worsening symptoms with no remissions; primary progressive MS where the symptoms progressively get worse with no remissions and progressive-relapsing MS which has progressive symptoms from onset with occasional flare-ups. Currently, modelling MS in animals can take two paths, each focusing on one of these drivers – the first focuses on the autoimmune component, where the experimental autoimmune encephalomyelitis (EAE) series of models are widely used. The other path focuses on studying mechanisms of demyelination independent of the autoimmune effects of MS where compounds such as cuprizone, lysolecithin and ethidium bromide induce demyelination.

The EAE series of models have been used extensively to study various hallmarks of MS including brain lesions and immune cell infiltration in the brain. Currently available drugs for MS have been tested in the EAE model and candidate drugs such as laquinimod have been shown to reduce the risk of disability progression in spontaneous EAE. The EAE model is useful for basic research to understand the development of the autoimmune response in MS but it is not optimal for testing therapies for MS. The current understanding in the field is that if a compound shows a strong effect in EAE models then further testing as an MS therapy is warranted but if a compound has a moderate or low effect in EAE models, then it is not advisable to pursue further testing. Therefore, the EAE model is essentially viewed as a method to eliminate compounds likely to fail in further testing as opposed to identifying compounds that can likely have a therapeutic effect.

Models of demyelination are gaining more importance for testing novel therapies for demyelination diseases independent of an immune response. Cuprizone is a copper chelator that has been reported to cause demyelination and has been shown to induce the death of oligodendrocytes possibly by altering cellular respiration and inactivating enzymes. Another model of demyelination involves the direct injection of lysolecithin into the spinal cord that is thought to induce phagocytosis of the myelin sheath. Ethidium bromide has been reported to induce demyelination in rat models by inducing lesion formation. Of the reported demyelination models, the cuprizone model is widely used as it is the easiest to induce (cuprizone is added to the animal diet). Cuprizone induces rapid demyelination but withdrawal results in rapid remyelination that can be delayed by the injection of rapamycin. Chronic demyelination can be induced in C57BL/6 mice maintained on a cuprizone diet for 12 weeks but the mice do not live past 16 weeks so the window to perform efficacy studies is short.

Researchers are investigating new approaches to develop improved models of MS especially for the progressive form of disease. One option is to use non-rodent species such as zebrafish that are emerging as a useful model to study demyelination since changes in live neurons can be easily detected in the transparent fish. Another approach is to develop improved rodent models with better defined endpoints to detect changes induced by demyelination. Preclinical modelling of MS is challenging but given the unmet clinical need there is an impetus to improve available preclinical models, especially for progressive MS. **DDW**